Attorney Docket No. 038586-0393

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: U.S. Patent Application of:
Murray, *et al.*

Application No.: 10/587,313

Filed On: April 28, 2008

For: BONE MORPHOGENIC PROTEIN BINDING PEPTIDE

Examiner: David S. Romeo

Conf. No.: 4686

Art Unit: 1647

DECLARATION UNDER 37 C.F.R. 1.132

Commissioner for Patents
Alexandria, VA 22313-1450

Dear Sir:

I, Elsa Murray, Ph.D., hereby declare as follows:

1. I am a co-inventor of U.S. Application No. 11/985,745.

2. I am currently a Research Chemist in the Geriatric Research Education and Clinical Center at the Veterans Affairs Medical Center in Los Angeles, California. I received my Bachelor of Science degrees in zoology and chemistry from the University of Nevada, Las Vegas. I received my Ph.D. in biochemistry from the University of Minnesota, Minneapolis.

3. The present invention relates to BBP ("BMP Binding Peptide"), an isolated peptide comprising the amino acid sequence of SEQ ID NO: 1 or a fragment thereof, wherein the peptide or fragment increases the degree or rate of osteogenesis or calcification.

4. I have reviewed the Office Action issued on August 30th, 2011 in this case. I have also reviewed U.S. Patent No. 5,620,867 ("Kiefer") and WO 96/21006 ("Price").

5. For the purpose of clarification, I would like to note that Kiefer and Price actually relate to the bovine spp24 peptide, which is not a BMP. *See* Brochmann, E. J., *et al.*, *Bone morphogenetic protein-2 activity is regulated by secreted phosphoprotein-24 kd, an extracellular pseudoreceptor, the gene for which maps to a region of the human genome important for bone quality*, 58 Metabolism 644 (2009)("Brochmann 2009"). Kiefer and Price incorrectly refer to the spp24 peptide and its fragments as "BMP." *See id.* I will refer to the peptide and peptide fragments discussed in these references as spp24, even though Price and Kiefer refer to these peptides as "BMP."

6. I understand that Kiefer and Price provide the sequence of bovine spp24, and as a result the Examiner contends that Kiefer discloses the claimed peptide comprising SEQ ID NO: 1 or a fragment thereof. While Kiefer does provide the sequence of bovine spp24 in Figure 3, and Price provides the sequence of bovine spp24 in Figure 5, neither Kiefer nor Price teach a fragment of spp24 that induces bone formation.

7. Kiefer speculates that peptides having the sequence described in Figures 3 and 5 are pro-osteogenic. *See* Kiefer, at 1:15-19; 1:58; 9:34-51; 11:4-16; 12:6-10; 20:5-24. Kiefer does not provide examples of specific fragments of spp24 that are pro-osteogenic, and Kiefer does not specifically teach that the BBP peptide is pro-osteogenic. *Id.* In fact, fragments of substantially purified spp24 that have been tested have been shown to *inhibit* bone formation, with the exception of the claimed BBP peptide. Additionally, Price does not provide any data showing that spp24, or fragments thereof, are pro-osteogenic; to the contrary, spp24 inhibits bone formation.

8. In Kiefer, testing is described for Kiefer's recombinant peptides. In Example 7, Kiefer states that samples of purified recombinant spp24 were tested to determine whether they induced bone formation. Kiefer explains that the same level of positive results was observed with the recombinant spp24 as was previously noted with native "BMP" at equivalent concentrations, but the Kiefer patent does not

provide any data or other evidence and instead cites to a study contained in "Kawamura and Urist, Developmental Biology, 330 [*sic*], 435-442 (1982) [*sic*]" ("Kawamura"). Kiefer, at 20:10-13. I have reviewed the Kawamura article to which Kiefer cites, and the disclosure in Kawamura does not support the statements in Kiefer that the recombinant 18.5 kDa peptide was shown to induce bone formation.

9. Kawamura states that "BMP/NCP" was prepared from bovine cortical bone by differential precipitation. Kawamura, M., & Urist, M.R., "Growth Factors, Mitogens, Cytokines, and Bone Morphogenetic Protein In Induced Chondrogenesis In Tissue Culture," *Developmental Biology*, Vol. 130, pp. 435-442, at p. 436 (1988). Kawamura further explains that the "partially purified BMP" used in the experiment was obtained from bone through filtration, hydroxyapatite chromatography, and high-pressure liquid chromatography. I understand this disclosure to mean that a sample containing partially purified spp24 and fragments of this peptide, along with other peptide contaminants, was tested to determine whether the sample demonstrated osteogenic activity. The Kawamura article did not mention any testing of recombinant spp24 or fragments of spp24, and Kiefer provides no other data to support the conclusions stated in Example 7. Thus, Kiefer does not provide any support for the statements that Kiefer's recombinant peptides will be pro-osteogenic.

10. Furthermore, testing has shown that fragments of spp24, with the exception of the claimed BBP, *inhibit* bone formation. For example, in a study that examined whether spp18 induced bone formation, spp18 was administered in various concentrations in combination with BMP, and various concentrations of BMP were administered alone as controls. Sintuu, C., *et al.* "Full-Length spp24, but Not Its 18.5-kDa Proteolytic Fragment, Inhibits Bone-Healing in a Rodent Model of Spine Fusion," *The Journal Of Bone And Joint Surgery*, Vol. 93, pp. 1022-1032, at 1023-1024 (2011)("Sintuu 2011"). It was found that increasing doses of spp18 resulted in increased *inhibition* of bone formation. *Id.* at 1026-1027. For example, Figure 2 shows that increasing doses of spp18, when administered with

a higher dose of BMP, resulted in significant *inhibition* of bone formation. *Id.* at p. 1024. Thus, the results show that spp18 does not increase the degree or rate of osteogenesis when administered with a BMP; rather, spp18 *inhibits* the degree or rate of osteogenesis when administered with a BMP.

11. Similarly, another study showed that spp24, spp18.1, spp16.0, and spp14.5, all fragments of spp24, did *not* induce bone formation when administered with BMP. *See* Brochmann, E.J., *et al.*, "Carboxy terminus of secreted phosphoprotein-24 kDa (spp24) is essential for full inhibition of BMP-2 activity," 28 *J. Orthopedic Research* 1200 (2010)("Brochmann 2010"). The results of this study showed that spp24, spp18.1, spp16.0, and spp14.5, when administered in varying concentrations along with BMP, either resulted in a *significant decrease* in bone formation or *did not induce bone formation. Id.*

12. The results obtained in the Sintuu 2011 study show that spp18 inhibits bone formation when administered in combination with BMP. *See* Sintuu 2011, at 1031-1032. This study also shows that spp18 is less inhibitory than full length spp24. *Id.* However, the fact that spp18 is *less inhibitory* than the full-length spp24 *does not mean* that spp18 is pro-osteogenic. This is because spp18 *still produces less bone formation than that observed with BMP alone.* In contrast, the claimed BBP peptide, administered in combination with BMP, results in a *greater amount of bone formation* than that observed with BMP alone. *See* Patent Application, at Example 2. Thus, the administration of BBP peptide in combination with BMP produces an *unexpected* synergistic effect, compared to the result obtained after administration of spp18 and BMP or the administration of spp24 and BMP. As explained above, this result was *very surprising*, since every other spp24 fragment tested either *inhibited* bone formation or *did not induce bone* formation.

13. In my opinion, as explained above, neither Kiefer nor Price disclose a peptide fragment of bovine spp24 that is pro-osteogenic. Testing has shown that *all fragments of spp24 tested*, except the claimed BBP, *inhibit bone formation.*

Therefore, neither Kiefer nor Price disclose, inherently or otherwise, a fragment of spp24 that is pro-osteogenic.

Respectfully submitted,

Elsa J. Brochmann Murray

Dated: Dec. 16, 2011

Elsa J. Brochmann Murray, Ph.D.

Enclosures: